Women and Ischemia Syndrome Evaluation (WISE)
Diagnosis and Pathophysiology of Ischemic Heart Disease
Workshop

October 2-4, 2002

Session 2

1. Topic and Author

Pain Threshold and Perception (Gender Differences)
David S. Sheps, MD, MSPH

2. Where we stand in 2002. Overview/rationale for inclusion of topic.

Gender differences in the pathophysiologic treatment in course of coronary artery disease (CAD) have been described extensively. It is well known that accurate diagnosis of CAD in women remains challenging. As early as 1986 reports from the Framingham study[1] showed that there were discrepancies in the number of women and men reporting angina followed by myocardial infarction. Recent evidence suggests that substantial obstacles to treating coronary disease in women still exist. This disparity may be due in part to the difficulty in evaluating chest pain in women whose assessments often are characterized by an increased prevalence of false positive exercise tests, false positive radionuclide tests, and substantial sex bias.

There is a substantial body of literature on differences in pain threshold and perception with mixed findings. Recently, Riley, et al. [2], reported on a Meta analysis of sex differences in the perception of noxious experimental stimuli. They reported on studies using quantitative evidence to address the magnitude of sex differences in response to experimentally induced pain. Their conclusions were that the effect size ranges from large to moderate depending on whether threshold or tolerance was measured and which method of stimulus administration was used. The values for pressure pain and electrical stimulation were the largest. For studies employing a threshold measure, the effect for thermal pain was smaller and more variable. Many studies failed to reject the null hypothesis due to the lack of power from insufficient number of subjects. Riley et al.[2] concluded that given an appropriately estimated effect size of .55 for threshold or .57 for tolerance, 41 subjects per group are necessary to provide for adequate power (0.70) to test for this difference.

While the clinical relevance of experimental studies may be questioned, data from clinical studies reveal a similar gender difference in the reporting of clinical pain syndromes. For example, women have a higher prevalence of migraine and non-migrainous headache, temporal mandibular disorders and back pain[3]. In addition, we have recently described gender differences in chest pain reporting in patients with CAD; women report more chest pain during daily life and during mental stress[4]. We have also shown that in women with coronary artery disease, individuals with low hot pain thresholds also have shorter time to exercise induced angina[5]. Thus, not only are gender differences in pain perception in the laboratory mimicked by differences in clinical pain experiences, but clinical pain is also related to sensitivity to experimental pain stimuli at least in patients with CAD. Women have lower threshold and tolerance and exhibit different mechanisms. Mechanisms underlying gender-related differences in pain perception have been explored. One explanation for the gender differences is that there are sex differences at the level of endogenous pain modulatory systems. A number of animal studies have provided evidence that there are sex differences in opioid activity that mediate analgesic responses to noxious stimuli. Evidence from human studies is more controversial.

In Maixner and Humphries[6] work blood pressure was related to pain ratings in men but not in women. We have shown higher levels of circulating beta endorphins in hypertensive humans relative to normotensives[7].

In 196 patients with documented CAD studied by the Psychophysiological Investigations in Myocardial Ischemia

Study (PIMI), the Marstork test of cutaneous sensory perception was administered at baseline and after exercise and mental stress. Patients with significantly lower hot pain threshold (less than 41° C) had significantly shorter time to angina onset on exercise testing than patients with hot pain threshold greater than 41° C ($p<.04$ log rank test). When looking at gender differences in the low and the high hot pain threshold group, there were significantly more females than males in the low hot pain threshold group (33% vs. 10% $p < .01$).

In another report from the PIMI Study, we specifically evaluated gender differences in chest pain in patients with documented CAD and exercise-induced ischemia. We studied chest pain reporting during daily activities, exercise, and mental stress in 170 men and 26 women[4]. All patients had documented CAD (>50% narrowing in at least one major coronary artery or prior myocardial infarction) and all had a positive treadmill exercise test. Women reported chest pain more often than men during daily activities $p=.04$) and during laboratory mental stressors, $p=.01$ but not during exercise. Men had lower scores than women on measures of depression, trait anxiety, harm avoidance and reward dependence. Women had significantly lower plasma beta endorphin levels at rest (4.2 ± 3.9 vs. 5.0 ± 2.5 pmol/liter for men $p=.005$) and at maximal mental stress (6.4 ± 5.1 vs. 7.4 ± 3.5 pmol/liter for men $p < .01$). These results from the PIMI population of patients with clinically documented CAD support the existence of gender differences in the affective and discriminative aspects of pain perception and may help explain gender-related differences in clinical presentations.

3. Current challenges and the most important issues for future research

As delineated in the previous section, it is clear that there are differences in pain threshold and perception between males and females. The challenge for the future is to further define the mechanisms of those differences and to translate further knowledge in mechanisms to improvements in clinical diagnosis and treatment. For example, although women have more frequent symptoms than men, a critical challenge for the future is to identify the types of symptoms or the types of individuals that will be more closely linked with the production of clinical events in the future. We know that ischemia in patients with coronary disease which is precipitated by mental stress is predictive of an increased risk for future events[8]. However, there is no clinically standardized way to identify these individuals. More research therefore needs to be done in identifying common clinical tests which can be applied to a high-risk population of patients with known ischemic heart disease and other tests which will be useful in separating patients with symptoms who have or do not have underlying coronary disease.

4. Current challenges in the areas of communicating messages to health care community, patients and the public

The major challenges in this area are the following: 1) identifying patients with atypical chest pain who have underlying coronary disease; 2) learning more about patients with microvascular or endothelial dysfunction in terms of their risk for future events; 3) identifying the best approach to treatment for the large majority of patients who have no significant underlying cardiac disease but continue to have symptoms.

5. Translating new findings to improved diagnosis and treatment/saving lives.

New research findings eventually need to be translated to the clinical arena.

1. Mental stress induced ischemia needs to be more commonly identified in patients with underlying coronary disease.
2. The clinical relevance of abnormalities in pain perception testing to pathophysiology and progression of disease needs to be further explored, i.e., are patients who have low pain thresholds and shorter time to angina at higher risk for future cardiac events?

6. References.

1. Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. Am Heart J 111:383-90, 1986.

2. Riley JL, Robinson ME, Wise EA, Myers CD, Fillingim RB: Sex differences in the perception of noxious

experimental stimuli: A meta-analysis. Pain 74:181-187, 1998.

3. Fillingim RB, Maixner W. Gender differences in the responses to noxious stimuli. Pain Forum 4(4):209-21, 1995.

4. Sheps DS, Kaufmann PG, Sheffield D, Light KC, McMahon RP, Bonsall R, Maixner W, Carney RM, Freedland KE, Cohen JD, Goldberg AD, Ketterer MW, Raczynski JM, Pepine CJ for the PIMI Investigators: Sex differences in chest pain in patients with documented coronary artery disease and exercise-induced ischemia: Results from the PIMI study. Am Heart J 142(5):864-871, 2001.

5. Sheps DS, McMahon RP, Light KC, Maixner W, Pepine CJ, Cohen JD, Goldberg AD, Bonsall R, Carney R, Stone PH, Sheffield D, Kaufmann PG, and the PIMI Investigators. Low hot pain threshold predics shorter time to exercise-induced angina: Results from the Psychophysiological Investigations of Myocardial Ischemia (PIMI) Study. J Am Coll of Cardiol 33(7):1855-62, 1999.

6. Maixner W, Humphrey C. Gender differences in pain and cardiovascular responses to forearm ischemia. Clin J Pain 8:16-25, 1993.

7. Sheps DS, Bradgon EE, Gray TF, Ballenger MN, Usedom JE, Maixner W. Relation between systemic hypertension and pain perception. Am J Cardiol 70:3F-5F, 1992.

8. Sheps DS, McMahon RB, Becker L, Carney RM, Freedland KE, Cohen JD, Sheffield D, Goldberg AD, Ketterer MW, Pepine CJ, Raczynski JM, Light K, Krantz DS, Stone PH, Knatterud GL, Kaufmann PG. Mental stress-induced ischemia and all-cause mortality in patients with coronary artery disease. Circulation 105:1780-84, 2002.